REMARKS

The Official Action dated April 5, 2004 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claim 1 is amended to include the limitation of claim 33, and claim 33 is cancelled. Claim 11 is amended to correspond with claim 1 as amended. It is believed that these changes do not involve any introduction of new matter, or raise any new issues subsequent to final rejection, whereby entry is believed to be in order and is respectfully requested.

Claims 1-3, 6, 11-18, 20-25 and 27-39 have been rejected as being obvious and unpatentable over the Rylatt et al PCT application WO 97/09620 in view of the Van Deusen et al U.S. Patent No. 5,132,097. The Examiner asserted that Rylatt et al disclose a lateral flow permeable medium comprising a calibration zone and a test/detection zone wherein the test/detection zone is downstream of the calibration zone, and the Examiner referred to Figures 2, 5 and 8. The Examiner acknowledged that Rylatt et al fail to teach that the calibrator and the analyte biospecifically bind to Reactant* by equivalent binding sites. However, the Examiner relied on Van Deusen et al as disclosing a test strip with a standard area/calibration zone and a test area/detection zone wherein a labeled reagent binds to both calibrator and analyte. In response to Applicants' previous arguments, the Examiner asserted that claim 20 only recites one calibration zone and one detection zone downstream of the one calibration zone.

However, Applicants submit that the methods and devices defined by claims 1-3, 6, 11-18, 20-25, 27-32 and 34-39 are nonobvious over and patentably distinguishable from

Rylatt et al in view of Van Deusen et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, as defined by claim 1, the invention is directed to a lateral flow method for the determination of an analyte in a sample using biospecific affinity reactions. The method comprises forming a complex in a lateral flow matrix, the complex comprising Reactant I---Analyte'---Reactant*, where Reactant* and Reactant I exhibit biospecific affinity to the analyte, Reactant* is analytically detectable, and Analyte' is the analyte or an analyte-related reactant. The method further comprises subsequently determining a detectable signal constituting a sample value from Reactant* in the complex, and determining the amount of analyte in the sample by comparing the sample value with one or more calibrator values, each of which corresponds to a standard amount of analyte. Before determination of the calibrator value, either (i) calibrator, or (ii) a binder for the calibrator has been bound to a matrix, and when a binder for the calibrator has been bound to the matrix, calibrator is added or calibrator predeposited in the matrix is released for binding with the binder, and the matrix is insoluble in the liquid medium in which binding of Reactant* to the calibrator occurs. The calibrator and the analyte exhibit biospecific affinity to Reactant* by equivalent binding sites. One or more calibrator zones CZ comprising calibrator or binder for the calibrator are located in a single process flow stream with Reactant I in a detection zone DZ, and all of the detection zones DZ are downstream of all of the calibrator zones CZ in the lateral flow matrix.

As defined by claim 20, the invention is directed to a device for transforming measured signal values of a complexed, analytically detectable reactant (Reactant*) to real amounts of analyte in a sample, in connection with performing an analysis method using biospecific affinity reactions for the determination of the amount of analyte in a sample, to form complexes comprising Reactant* in an amount which is related to the amount of analyte in the sample. The device comprises a flow matrix in which there is an area of process flow

for the transport of Reactant*. In the process flow area are (i) one or more calibrator zones (CZ) comprising a calibrator, or binder for the calibrator, which is firmly anchored to the matrix, the amounts of calibrator or calibrator binder, respectively, being different for at least two calibrator zones when at least two calibrator zones are present, and the calibrator exhibiting binding sites to which Reactant* binds, when Reactant* is transported through a calibrator zone, (ii) an application zone for Reactant* ($A_{R*}Z$) upstream of the calibrator zones, and (iii) one or more detection zones (DZ). All of the detection zones are downstream of all of the calibrator zones.

The methods and devices according to the present invention provide improvements in analyte determinations employing calibrators. Particularly, the present methods enable compensation for the differences that may exist between calibrator and sample solution and between runs performed at different times and/or different places. These advantages are obtained by the defined methods of claim 1, employing Reactant* which binds to either analyte or calibrator, and forming the complex in the flow matrix and wherein the calibrator zone or zones are located in the same process flow as the detection zone for measuring analyte. Similarly, these advantages are obtained by the defined methods and devices of claims 1 and 20, employing one or more calibrator zones and one or more detection zones, with *all* of the detection zones being downstream of *all* of the calibrator zones. Further, according to claim 20, the calibrator exhibits binding sites to which Reactant* binds when Reactant* is transported through a calibrator zone, and an application zone for Reactant* is upstream of the calibrator zones.

Rylatt et al disclose a method and device for determination of an analyte in a sample. With reference to Fig. 2 cited by the Examiner, the Rylatt et al device includes a test zone 204 arranged between calibration zones 210 and 211. Thus, *all* of the detection or test zones are not downstream of *all* of the calibration zones as required by claims 1 and 20, but

interspersed therein. Moreover, Applicants find no teaching or suggestion by Rylatt et al of a method or device employing Reactant* as presently claimed, binding to both calibrator and analyte as recited in claim 1. Rather, as shown in Fig. 2 of Rylatt et al, the procedure of Rylatt et al employs an analyte detection agent 208 for binding in the test zone and a separate calibration agent 209 for binding in the calibration zone. Further, the procedure described in Fig. 2 of Rylatt et al employs a separate support element for diffusibly attaching the analyte detection agent 208 and the calibration agent 209, and Applicants find no teaching or suggestion by Rylatt et al as to where such elements would be provided in the flow matrix 207.

In response to Applicants' previous arguments, the Examiner asserted that claim 20 only requires the presence of one calibration zone and one detection zone and that Rylatt et al clearly teach one calibration zone and one detection zone downstream of the one calibration zone. However, the Examiner's rationale ignores the express limitations of claims 1 and 20, namely, that *all of the detection zones DZ are downstream of all of the calibrator zones CZ in the lateral flow matrix.* Thus, according to claims 1 and 20, if more than one calibrator zone is employed, all of the detection zones DZ are downstream of all of the calibrator zones CZ in the lateral flow matrix. To the contrary, Rylatt et al do not teach all of the detection zones downstream of all of the calibrator zones, as test zone 204 is arranged between calibration zones 210 and 211. Thus, Rylatt et al expressly teach away from the presently claimed methods and devices. It is error to find obviousness where references diverge from and teach away from the invention at hand, *In re Fine*, 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). Thus, it is error to find obviousness of the presently claimed methods and devices based on Rylatt et al.

The Examiner has relied on Van Deusen et al to resolve the deficiencies of Rylatt et al. Van Deusen et al disclose a test strip including a standard or control area 16 containing a

known amount of Reactant B (analyte) bound to Reactant A. The test strip is adapted for placement in a test solution containing a test sample (column 4, lines 22-25) and, subsequently, in a solution containing an identifier, for example, bound to a microbead (column 4, lines 34-38). Van Deusen et al provide no teaching or suggestion relating to a lateral flow method or device or for improving reliable calibration in lateral flow techniques. Further, Applicants find no teaching or suggestion by Van Deusen et al for replacing the distinct labeled calibration agent/calibration agent receptor binding pair of Rylatt et al with a calibrator as presently claimed, which together with analyte exhibits biospecific affinity to Reactant* by equivalent binding sites. Only in hindsight of the presently claimed methods would one of ordinary skill in the art be motivated to combine the teachings of Van Deusen et al, which are more specifically directed to the use of a laser for detecting a light pattern through the reactive surface, with the lateral flow method and apparatus of Rylatt et al in order to obtain the advantage of avoiding process variations between testing and calibration which are avoided according to the present methods and devices.

Moreover, if the teachings of Van Deusen et al are combined with Rylatt et al as asserted by the Examiner, such a combination does not result in either the method of claim 1 or the device of claim 20. That is, neither Rylatt et al nor Van Deusen et al teach a lateral flow matrix method wherein a single analytically detectable reactant may be employed, as in claim 1. Moreover, neither Rylatt et al nor Van Deusen et al teach a lateral flow method or device employing a lateral flow matrix wherein all detection zones are downstream of all calibration zones.

In reply to Applicants' previous arguments that Van Deusen et al and Rylatt et al are not properly combinable, the Examiner asserts that because Van Deusen et al show the use of their labeled reagent provides for a standard area and a test area having both calibrator and analyte produced on the same test strip and provide for a method in which it is not necessary

for the reactants to come to equilibrium, the asserted combination is proper. However, the Examiner disregards the significant distinction that the Van Deusen et al test strip is adapted for placement in a test solution and subsequent placement in a solution containing identifier, and that Van Deusen et al provide no teachings or suggestions relating to lateral flow techniques. Those skilled in the art will recognize that lateral flow methodology and devices are not simply interchangeable with solution assay techniques as described by Van Deusen et al. Thus, the teachings of Van Deusen et al relied upon by the Examiner would not have motivated one of ordinary skill in the art to make the substitutions in the teachings of Rylatt et al in the absence of the teachings of the present application and claims.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some teaching, suggestion or incentive supporting the combination, *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987). Rylatt et al and Van Deusen et al provide no teaching, suggestion or incentive for combining their teachings along the lines of the presently claimed method and device, and particularly provide no teaching or suggestion of all of the limitations of claims 1 and 20, or the advantages taught in the present specification. Thus, Rylatt et al and Van Deusen et al do not render the presently claimed method and device obvious. It is therefore submitted that the methods and devices defined by claims 1-3, 6, 11-18, 20-25, 27-32 and 34-39 are nonobvious over and patentably distinguishable from the combination of Rylatt et al and Van Deusen et al, whereby the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

Claim 19 has been rejected as being obvious and unpatentable over Rylatt et al and Van Deusen et al in view of the Self et al U.S. Patent No. 4,446,231. The Examiner relied on Self et al as teaching diagnosis of an autoimmune disease.

However, Applicants submit that the methods defined by claim 19 are nonobvious over and patentably distinguishable from the teachings of Rylatt et al, Van Deusen et al and Self. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The deficiencies of Rylatt et al and Van Deusen et al with respect to claim 1, on which claim 19 depends, are discussed in detail above. Self does not resolve these deficiencies. That is, Self discloses an immunoassay employing an enzyme label which converts a precursor into a cycling factor which in turn is interconverted in a cycling detection system. Applicants find no teaching or suggestion by Self relating to a lateral flow method wherein a complex is formed in a lateral flow matrix using Reactant* to which both analyte and calibrator bind as defined in present claim 1 and employing one or more calibration zones, in the same process flow as a detection zone, with all detection zones downstream of all calibrator zones.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). In view of the failure of Rylatt et al, Van Deusen et al and Self to teach a lateral flow method as claimed, the combination of these references does not enable one of ordinary skill in the art to conduct the method of claim 1 and therefore does not render claim 1, or claim 19 dependent thereon, obvious. It is therefore submitted that the rejection of claim 19 under 35 U.S.C. §103 based on Rylatt et al, Van Deusen et al and Self has been overcome. Reconsideration is respectfully requested.

Claims 4 and 26 have been rejected as being obvious and unpatentable over Rylatt et al and Van Deusen et al in view of the Weng et al U.S. Patent No. 4,740,468. The Examiner relied on Weng et al as disclosing the use of a specific binding partner that is biospecific to a second binding partner which in turn is specific for an analyte. The Examiner asserted it

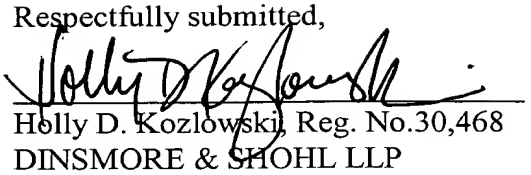
would have been obvious to incorporate an immobilized specific binding partner as taught by Weng et al in the device of Rylatt et al.

However, Applicants submit that the method and device defined by claims 4 and 26 are nonobvious over and patentably distinguishable from the combination of Rylatt et al, Van Deusen et al and Weng et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The deficiencies of Rylatt et al and Van Deusen et al have been discussed above with respect to claim 1 and claim 20, on which claim 4 and claim 26 depend, respectively, and are not resolved by Weng et al. That is, Weng et al disclose a method and device for determining the presence of an analyte in a sample suspected of containing the analyte. Applicants find no teaching or suggestion by Weng et al for modifying the device of Rylatt et al in accordance with the method and device as recited in claims 1 and 20, wherein all of the the detection or test zones are downstream of the all of the calibration zones, a single Reactant* as presently claimed, binding to both calibrator and analyte, is employed in a lateral flow matrix, and/or where such Reactant* is arranged in the flow matrix. Thus, Weng et al do not resolve the deficiencies of Rylatt et al and Van Deusen et al. It is therefore submitted that the rejection under 35 U.S.C. §103 based on these references has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the rejections under 35 U.S.C. §103 and places the present application in condition for allowance. Reconsideration and an early allowance are requested. In the event that the present application is still not in condition for allowance, entry of the present amendment for purposes of appeal is requested.

Respectfully submitted,



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